

**REMARKS**

Claims 1-4, 8, 9, and 32 have been cancelled without prejudice. Claim 33 has been amended. Claims 33-35, 39-43 and 47-49 presently are pending and under consideration.

Support for the amendment to claim 33, which now recites that the anti-angiogenesis factor and the tetrapyrrole derivative are “not coupled to one another” is found throughout the specification and claims as originally filed. For example, support can be found at page 19, second paragraph, lines 25-27, Example 1, and page 12, lines 28-30 of the application as filed. Applicants believe that the amendment introduces no new matter.

The undersigned wishes to inform the Office that the undersigned attorney has left Testa, Hurwitz, and Thibeault, LLP and is now located at Goodwin Procter, LLP, Exchange Place, 53 State Street, Boston, MA 02109. The Office is requested to mail all subsequent papers to the attention of the Patent Administrator, Goodwin Procter, LLP, Exchange Place, 53 State Street, Boston, MA 02109. The undersigned is in the process of having a new customer number assigned to the case.

**Rejections Under 35 U.S.C. §103(a)**

*According to section 5 of the outstanding Office Action*, claims 1-4, 8, 9, 32-35, 39-43 and 47-49, which are directed to methods of treating unwanted choroidal neovasculature, presently stand rejected for obviousness over U.S. Patent No. 6,270,749 (hereafter “the ‘749 patent”) in view of Adamis *et al.* (Arch. Ophthalmol. 114:66-71, 1996; hereafter “Adamis”) and in view of U.S. Patent No. 6,342,219 (hereafter “the ‘219 patent”). Claims 1-4, 8, 9 and 32 have been cancelled without prejudice. Applicants respectfully traverse this rejection to the extent that it is maintained over the claims, as amended, for the following reasons.

To establish a *prima facie* case of obviousness under §103, the Office must demonstrate that the differences between the claimed invention and the prior art are such that the subject matter as a whole would have been obvious, at the time the invention was made, to a person having ordinary skill in the art. *In re Dembicza*k, 175 F.3d 994, 998, 50 USPQ2d 1614, 1616 (Fed. Cir. 1999). This requires a comparison of the claimed subject matter “as a whole” with the

prior art “to which said subject matter pertains.” 35 U.S.C. §103(a). Furthermore, where claimed subject matter is rejected as obvious in view of a combination of references “there must be some motivation, suggestion or teaching of the desirability of making the specific combination that was made by the applicant” in the cited references. *In re Kotzab*, 217 F.3d 1365, 1369-70, 55 USPQ2d 1313, 1316 (Fed. Cir. 2000). Even if every element of a claimed invention is identified in the prior art, this alone is insufficient to establish obviousness. *In re Roufett*, 149 F.3d 1350, 1357, 47 U.S.P.Q.2d 1453, 1457-1458 (Fed. Cir. 1998). To support an obviousness rejection over a combination of references, the Office must show that a skilled artisan, when confronted with the same problem as Applicants, would choose all of the elements of the invention and combine them in the manner claimed. *In re Roufett*, 149 F.3d 1350, 1357, 47 U.S.P.Q.2d 1453, 1457-1458 (Fed. Cir. 1998). For the following reasons, Applicants respectfully submit that the claimed invention would not have been obvious to the skilled artisan relying on the teachings of the applied references at the time the invention was made.

The method of claim 33 is directed to a method of treating unwanted choroidal neovasculature comprising endothelial cells in a mammal. The method comprises the steps of: (a) administering to the mammal an anti-angiogenesis factor in an amount sufficient to permit an effective amount to localize in the choroidal neovasculature, wherein the anti-angiogenesis factor is selected from the group consisting of angiostatin and an antibody that binds preferentially to vascular endothelial growth factor; (b) administering to the mammal an amount of a tetrapyrrole derivative photosensitizer sufficient to permit an effective amount to localize in the choroidal neovasculature, wherein the photosensitizer is selected from the group consisting of lutetium texaphyrin and benzoporphyrin derivative, *and wherein the anti-angiogenesis factor and the tetrapyrrole derivative photosensitizer are not coupled to one another*; and (c) irradiating the choroidal neovasculature with laser light such that the light is absorbed by the photosensitizer so as to occlude the choroidal neovasculature, *wherein the occlusion caused by step (a) is synergistic with the occlusion caused by steps (b) and (c)*.

The method of claim 41 also is directed to a method of treating unwanted choroidal neovasculature comprising endothelial cells in a mammal. The method comprises the steps of:

(a) administering to the mammal an anti-angiogenesis factor in an amount sufficient to permit an effective amount to localize in the choroidal neovasculature, wherein the anti-angiogenesis factor is selected from the group consisting of angiostatin and an antibody that binds preferentially to vascular endothelial growth factor; (b) administering to the mammal *after step (a)* an amount of a tetrapyrrole derivative photosensitizer sufficient to permit an effective amount to localize in the choroidal neovasculature, wherein the photosensitizer is selected from the group consisting of lutetium texaphyrin and benzoporphyrin derivative; and (c) irradiating the choroidal neovasculature with laser light such that the light is absorbed by the photosensitizer so as to occlude the choroidal neovasculature, *wherein damage to the endothelial cells resulting from the combination of steps (a), (b), and (c) is greater than that resulting only from the sum of steps (a), (b) and (c)*. In this claim, the anti-angiogenesis factor and the photosensitizer are not coupled or conjugated to one another because the photosensitizer is administered after the anti-angiogenesis factor.

The primary reference, the '749 patent, describes the use of photosensitive texaphyrins during photodynamic therapy for the treatment of choroidal neovasculature. The '749 patent mentions that the texaphyrin photosensitizer can be coupled or conjugated to a targeting moiety, for example, "molecules directed at vascular endothelial growth factor (VEGF)," see column 10, lines 48-50 of the '749 patent. The '749 patent merely discusses these molecules in the context of targeting and nowhere suggests administering an anti-VEGF antibody to the recipient to reduce or inhibit the formation of new blood vessels in the recipient.

Applicants submit that the skilled artisan would not have been motivated to adapt the methods of the '749 patent to arrive at Applicants' invention. The targeting occurs when the targeting moiety is coupled or conjugated to the photosensitizer. Applicants submit that the skilled artisan would not have been motivated to administer the targeting moiety and photosensitizer as unconjugated entities as this would effectively undermine the purpose of benefit of having a targeting moiety. In effect, the '749 patent teaches away from the claimed invention of using a photosensitizer not coupled or conjugated to the anti-angiogenesis factor.

Furthermore, Applicants submit that the method of claim 33 further requires that the “occlusion caused by step (a) is synergistic with the occlusion caused by steps (b) and (c).” Also, Applicants submit that the method of claim 41 further requires that the damage to the endothelial cells resulting from the combination of steps (a), (b), and (c) is greater than that resulting only from the sum of steps (a), (b) and (c). Applicants submit that such features of the claimed method are neither taught nor suggested in the ‘749 patent. Applicants submit that the secondary references (i.e., Adamis and the ‘219 patent) fail to make up for the deficiencies in the ‘749 patent.

Adamis describes the use of an anti-VEGF monoclonal antibody to prevent iris neovascularization following retinal ischemia in non-human primates. Adamis, however, fails to teach or suggest combining an anti-VEGF antibody with a photodynamic therapy-based treatment of unwanted choroidal neovasculature. Furthermore, Applicants submit that Adamis teaches the treatment of iris not choroidal neovascularization of the eye, as required by the claimed invention.

The ‘219 patent describes the use of anti-VEGF antibodies that inhibit VEGF binding to a VEGF receptor, and the use of such antibodies for the treatment of choroidal neovascularization. The ‘219 patent, however, fails to teach or suggest combining the anti-VEGF antibody with a photodynamic therapy-based treatment of unwanted choroidal neovasculature.

Applicants submit that there is nothing in any of the applied references that would motivate the skilled artisan to combine their respective teachings to arrive at a method wherein the anti-angiogenesis factor and photosensitizer are not coupled or conjugated to one another. For the sake of argument only, even if the teachings of Adamis, the ‘219 patent and the ‘749 patent were combined in the manner suggested in the Office Action, Applicants submit that their combined teachings fail to teach or suggest a method where occlusion caused by administering an anti-angiogenic factor, i.e., step (a), is synergistic with the occlusion caused by photodynamic therapy, i.e., steps (b) and (c), as required by claim 33. Similarly, Applicants submit that their combined teaching fail to teach or suggest a method where the damage to the endothelial cells resulting from the combination of photodynamic therapy and administration of and anti-

angiogenic factor (i.e., steps (a), (b), and (c)) is greater than that resulting only from the sum of steps (a), (b) and (c), as required by claim 41.

Contrary to the Examiner's assertion that "there is no evidence that the method of use described in the instant claims would differ in an unexpected manner from those described in the references," Applicants disclose in their specification that angiostatin and Lu-Tex showed a synergistic cytotoxic effect on BRCE endothelial cells (see, page 25, first paragraph, lines 7-10). The effect of this combination exceeded the cytotoxicity of either treatment alone, and also exceeded the arithmetic sums of their respective toxicities. The surprising effectiveness of this combination could not have been predicted by the skilled artisan based on teachings present in any of the references replied upon by the Examiner in the outstanding Action.

Furthermore, the claimed combination is also effective *in vivo* for the treatment of choroidal neovascularization as evidenced in an abstract (made of record as citation C115), which was presented in May of 2003 at the Annual Meeting of the Association of Research in Vision and Ophthalmology in Fort Lauderdale, Florida. The abstract describes experiments that were carried out using methods taught in Applicants' specification (e.g., pages 3-4, page 8, paragraph 3, and pages 13-17). These experiments showed that under the conditions tested, the administration of angiostatin *on its own* did not prevent the growth of choroidal neovascular membranes. In contrast, *the combination* of angiostatin and PDT significantly increased the number of lesions without angiographic leakage. For example, 42.9% of the lesions tested lacked angiogenic leakage when treated only with PDT (photodynamic therapy) at 10J/cm<sup>2</sup>. In contrast 90-100% of the lesions tested lacked angiogenic leakage when treated with PDT at 10J/cm<sup>2</sup> when combined with angiostatin. Applicants have clearly shown that the claimed combination is unexpectedly effective in treating unwanted choroidal neovascularization *in vitro* and *in vivo*. These surprising results could not have been predicted based on any of the cited references.

In view of the foregoing, Applicants respectfully request that the rejection of claims 33 and 41, and the claims depending therefrom, be reconsidered and withdrawn.

*According to section 6 of the outstanding Office Action, claims 1-4, 8, 9, 32-35, 39-43 and 47-49, which are directed to methods of treating unwanted choroidal neovasculature, presently stand rejected for obviousness over Kramer *et al.* (Ophthalmol. 103:427-38, 1996; hereafter “Kramer”) in view of Adamis or the ‘219 patent. Claims 1-4, 8, 9 and 32 have been cancelled without prejudice. Applicants respectfully traverse this rejection to the extent that it is maintained over the claims, as amended, for the following reasons.*

The primary reference, Kramer, describes the use of liposomal benzoporphyrin derivative (BPD) verteporfin photodynamic therapy for the treatment of choroidal neovascularization in monkeys. Kramer, however, fails to teach or suggest the additional step of combining an anti-angiogenesis factor during photodynamic therapy. Applicants submit that the secondary references (Adamis and the ‘219 patent) fail to make up for the deficiencies in Kramer.

Adamis describes the use of an anti-VEGF monoclonal antibody to prevent iris neovascularization following retinal ischemia in non-human primates. Applicants submit, however, that Adamis fails to teach or suggest combining the anti-VEGF monoclonal antibody with photodynamic therapy. The ‘219 patent describes the use of anti-VEGF antibodies that inhibit VEGF binding to a VEGF receptor, and the use of such antibodies for the treatment of choroidal neovascularization. Applicants submit, however, that the ‘219 patent fails to teach or suggest combining the anti-VEGF antibody with photodynamic therapy.

Applicants submit that there is nothing in any of the applied references that would motivate the skilled artisan to combine their respective teachings to arrive at a method where an anti-angiogenesis factor is combined with a photodynamic therapy-based method for treating unwanted choroidal neovascularization. For the sake of argument only, even if the teachings of Kramer, Adamis, and the ‘219 patent were combined in the manner suggested in the Office Action, Applicants submit that their combined teachings fail to teach or suggest the claimed method taken as a whole where occlusion caused by administering an anti-angiogenic factor, i.e., step (a), is synergistic with the occlusion caused by photodynamic therapy, i.e., steps (b) and (c), as is required by claim 33. Similarly, Applicants submit that their combined teaching fail to teach or suggest a method where the damage to the endothelial cells resulting from the

combination of photodynamic therapy and administration of and anti-angiogenic factor (i.e., steps (a), (b), and (c)) is greater than that resulting only from the sum of steps (a), (b) and (c), as is required by claim 41.

The synergistic properties of the claimed invention were discussed previously and are again reiterated here. Applicants submit that teachings of the applied reference, either alone or in combination, fail to teach the claimed subject matter, taken as a whole, and Applicants respectfully request that this rejection of claims 33 and 41, and the claims depending therefrom, be reconsidered and withdrawn.

*According to section 7 of the outstanding Office Action*, claims 1-4, 8, 9, 32-35, 39-43 and 47-49, which are directed to methods of treating unwanted choroidal neovasculature, presently stand rejected for obviousness over Kramer in view of Adamis or the '219 patent and further in view of U.S. Patent No. 5,733,876 (the '876 patent). Claims 1-4, 8, 9 and 32 have been cancelled without prejudice. Applicants respectfully traverse this rejection to the extent that it is maintained over the claims, as amended, for the following reasons.

Kramer, Adamis, and the '219 patent were discussed previously and the comments are reiterated here. Applicants submit that the '876 patent fails to make up for the deficiencies in Kramer, Adamis and the '219 patent.

The '876 patent describes a method for inhibiting angiogenesis by administering angiostatin. The Office Action alleges that it would have been obvious for the skilled artisan to substitute angiostatin for the anti-VEGF antibody described by Adamis and the '219 patent, and to administer angiostatin in combination with the photosensitizer taught by Kramer. In support of this assertion, the Examiner cites column 10, lines 20-21, where the '876 patent states that “[a]ngiostatin may be used in combination with other compositions and procedures for disease.” The '876 patent, however, fails to even mention photodynamic therapy and, moreover, fails to teach or suggest the specific combination (i.e., a photosensitizer and an anti-angiogenesis factor), as required by the claimed invention. Accordingly, Applicants submit that the teachings of the '876 patent fail to remedy the shortcomings of Kramer, Adamis, and the '219 patent.

Applicants submit that there is nothing in any of the applied references that would motivate the skilled artisan to combine their respective teachings to arrive at the claimed method as a whole wherein an anti-angiogenesis factor (e.g., angiostatin) and a photosensitizer for photodynamic therapy are administered separately in a method for treating unwanted choroidal neovascularization. For the sake of argument only, even if the teachings of Kramer, Adamis, the '219 patent and the '876 patent were combined in the manner suggested in the Office Action, Applicants submit that their combined teachings fail to teach or suggest the claimed subject matter taken as a whole. For example, Applicants submit that the applied references fail to teach or suggest a method where occlusion caused by administering an anti-angiogenic factor, i.e., step (a), is synergistic with the occlusion caused by photodynamic therapy, i.e., steps (b) and (c), as is required by claim 33. Similarly, Applicants submit that their combined teaching fail to teach or suggest a method where the damage to the endothelial cells resulting from the combination of photodynamic therapy and administration of and anti-angiogenic factor, i.e., steps (a), (b), and (c) is greater than that resulting only from the sum of steps (a), (b) and (c), as is required by claim 41.

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*According to section 8 of the outstanding Office Action, claims 1-4, 8, 9, 32-35, 39-43 and 47-49, which are directed to methods of treating unwanted choroidal neovasculature, presently stand rejected for obviousness over Kramer in view of Adamis or the '219 patent and further in view of the '749 patent. Claims 1-4, 8, 9 and 32 have been cancelled without prejudice. Applicants respectfully traverse this rejection to the extent that it is maintained over the claims, as amended, for the following reasons.*

The primary reference, Kramer, describes the use of liposomal benzoporphyrin derivative (BPD) verteporfin photodynamic therapy for the treatment of choroidal neovascularization in

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Applicants submit that the '749 patent fails to make up for the deficiencies in Kramer, Adamis, and the '219 patent. The '749 patent, as discussed previously, describes the use of photosensitive texaphyrins conjugated or coupled to a targeting moiety, for example, molecules directed to VEGF, for photodynamic therapy of choroidal neovasculature. Applicants submit that the skilled artisan would not have been motivated to adapt the methods of the '749 patent to arrive at Applicants' invention. The targeting occurs when the targeting moiety is coupled or conjugated to the photosensitizer. Applicants submit that the skilled artisan would not have been motivated to administer the targeting moiety and photosensitizer as unconjugated entities as this would effectively undermine the purpose and benefit of having a targeting moiety. In effect, the '749 patent teaches away from the claimed invention of using a photosensitizer not coupled or conjugated to the anti-angiogenesis factor.

Applicants submit that there is nothing in any of the applied references that would motivate the skilled artisan to combine their respective teachings to arrive at a method wherein an anti-angiogenesis factor and a photosensitizer for photodynamic therapy are administered separately in a method for treating unwanted choroidal neovascularization. For the sake of argument only, even if the teachings of Kramer, Adamis, the '219 patent and the '749 patent were combined in the manner suggested in the Office Action, Applicants submit that their combined teachings fail to teach or suggest the claimed subject matter taken as a whole. For example, Applicants submit that the applied references fail to teach or suggest a method where

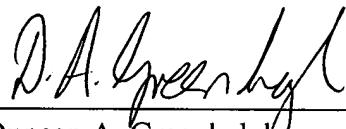
occlusion caused by administering an anti-angiogenic factor, i.e., step (a), is synergistic with the occlusion caused by photodynamic therapy, i.e., steps (b) and (c), as is required by claim 33. Similarly, Applicants submit that their combined teaching fail to teach or suggest a method where the damage to the endothelial cells resulting from the combination of photodynamic therapy and administration of an anti-angiogenic factor (i.e., steps (a), (b), and (c)) is greater than that resulting only from the sum of steps (a), (b) and (c), as is required by claim 41.

The synergistic properties of the claimed invention were discussed previously and are again reiterated here. Applicants submit that teachings of the applied reference, either alone or in combination, fail to teach the claimed subject matter, taken as a whole, and Applicants respectfully request that this rejection of claims 33 and 41, and the claims depending therefrom, be reconsidered and withdrawn.

## CONCLUSION

In view of the foregoing, Applicants respectfully request that the foregoing rejections be reconsidered and withdrawn. The Examiner is invited to contact the undersigned with any questions about this submission. Early favorable action is respectfully solicited.

Respectfully submitted,



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